Influenza A/H1N1 in patients with cystic fibrosis in Italy: a multicentre cohort study

The clinical consequences of influenza are severe in cystic fibrosis (CF), but the impact of A/H1N1 virus infection remains poorly defined. Pandemic influenza A/H1N1 started in Italy in September 2009 and CF patients were included among those at risk of complications and recommended to receive A/H1N1 vaccine. Better characterisation of the impact of influenza A/H1N1 in comparison with other flu-like illnesses in CF would provide a rational basis for antiviral treatment and vaccination strategies for the next flu season.

Within the Italian Cystic Fibrosis Society, we sent a questionnaire to 30 centres to collect follow-up data for all patients with influenza-like symptoms consecutively seen between November 2009 and March 2010. Realtime RT-PCR test was performed to define A/H1N1 status. Continuous variables are reported as medians, IQR (see online supplement for details of study methods).

Nineteen centres reported data from 127 patients: 68 were A/H1N1+ve and 59 were A/H1N1–ve for the RT-PCR test. Symptom onset peaked during calendar week 45 in A/H1N1+ve patients, similar to the general Italian population, whereas A/H1N1–ve patients showed a bimodal incidence peak at weeks 45 and 47 (online supplement).

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A/H1N1+ve patients tended to be younger than A/H1N1–ve patients (40% vs 58% aged ≥18 years; p = 0.051), with no other differences in clinical characteristics or symptoms leading to presentation to centres (online supplementary table S1).

Oseltamivir (2–3 mg/kg/day as currently recommended) was administered to 82% A/H1N1+ve and 12% A/H1N1–ve patients. In the A/H1N1+ve group, treatment was started within 24–48 h from symptom onset upon virological confirmation. Oseltamivir was well tolerated and no treatment cessation was required. In one A/H1N1+ve patient complications were associated with development of oseltamivir resistance.

Clinical course and duration of disease are reported in table 1. In the entire CF patient population, shorter disease duration was seen in oseltamivir treated patients (5, 4–11 vs 10, 6–14 days; p = 0.008), a difference apparently limited to the A/H1N1–ve subset.

Disease course was uncomplicated in 85% and 88% patients, respectively (p = 0.659). Of note, immunosuppressive therapy for organ transplantation did not increase risk of complications in either group.

Table 1 Clinical course of influenza illness and major complications according to the results of influenza A/H1N1 testing

<table>
<thead>
<tr>
<th></th>
<th>A/H1N1+ve (n = 68)</th>
<th>A/H1N1–ve (n = 59)</th>
<th>All patients</th>
<th>RR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of illness (days)*</td>
<td>5 (3–11)</td>
<td>10 (6–14)</td>
<td>7 (4–14)</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Pulmonary exacerbation†</td>
<td>46 (67.6%)</td>
<td>47 (79.7%)</td>
<td>93 (73.2%)</td>
<td>0.85 (0.69–1.05)</td>
<td>0.127</td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>47 (69.1%)</td>
<td>41 (69.5%)</td>
<td>88 (69.3%)</td>
<td>1.00 (0.79–1.25)</td>
<td>1.000</td>
</tr>
<tr>
<td>Antiviral therapy‡</td>
<td>56 (82.4%)</td>
<td>7 (11.1%)</td>
<td>63 (49.6%)</td>
<td>–0.0001</td>
<td></td>
</tr>
<tr>
<td>Complications</td>
<td>10 (14.7%)</td>
<td>7 (11.9%)</td>
<td>17 (13.4%)</td>
<td>1.24 (0.50–3.05)</td>
<td>0.795</td>
</tr>
<tr>
<td>Permanent need for oxygen therapy</td>
<td>1 (1.5%)</td>
<td>0</td>
<td>1 (0.8%)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>1 (1.5%)</td>
<td>1 (1.7%)</td>
<td>2 (1.6%)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>1 (1.5%)</td>
<td>0</td>
<td>1 (0.8%)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>2 (3.0%)</td>
<td>2 (3.4%)</td>
<td>4 (3.1%)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Atelectasis</td>
<td>0</td>
<td>1 (1.7%)</td>
<td>1 (0.8%)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>3 (4.4%)</td>
<td>1 (1.7%)</td>
<td>4 (3.1%)</td>
<td>2.60 (0.28–24)</td>
<td></td>
</tr>
</tbody>
</table>

*Among the 68 patients with A/H1N1 infection, duration of illness was 5 (3–9) days in the 56 patients treated with oseltamivir and 5 (3–11) days in the 12 patients who did not receive antiviral treatment (p = 0.874).
†Among the 68 patients with A/H1N1 infection, pulmonary exacerbations occurred in 69.6% of patients treated with oseltamivir and in 59.3% of those who did not receive antiviral therapy (p = 0.505).
‡Among the 68 patients with A/H1N1 infection, complications occurred in 17.9% of patients treated with oseltamivir and in none of those who did not receive antiviral therapy (p = 0.189).

Four patients with severe pulmonary disease (5 A/H1N1+ve, 1 A/H1N1–ve) died of respiratory failure: none had been vaccinated and all had received antiviral therapy (online supplementary table S2).

No significant FEV1 decline was observed in both groups after 1 and 6 months from symptom onset (online supplementary figure S2). In none of the cases, new isolation of Pseudomonas aeruginosa or Burkholderia cepacia complex was documented.

In conclusion, in a cohort of patients who consecutively presented to Italian CF centres for flu-like symptoms during the 2009 pandemic period, accurate diagnostic testing did not identify clinical characteristics specifically associated with A/H1N1 infection, the only exception being younger age in A/H1N1+ve patients. The use of a reliable identification method allowed appropriate treatment to be initiated.

Systematic collection of data at patient presentation and subsequent follow-up provided further information on A/H1N1 infection in CF, which will be useful to patients for the next influenza season.

Influenza A/H1N1 has no major impact in CF, but patients with poor clinical conditions due to the disease are exposed to substantial risk of complications and unfavourable outcomes. Annual vaccination for seasonal influenza and A/H1N1 influenza is recommended in CF, with continuing efforts towards higher vaccination coverage levels especially in adult subjects.

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